

EDITOR'S CHOICE

Neurosteroid therapy for Niemann-Pick Type C

Niemann-Pick type C (NP-C) is an autosomal recessive neurodegenerative lipid storage disorder that presents in childhood. 95% of cases result from mutations in the NPC1 gene that cause defective trafficking of intracellular cholesterol and subsequent lysosomal accumulation of unesterified cholesterol and glycosphingolipids. There is currently no therapy for this devastating disease, which leads to death in adolescence.

There is a naturally occurring mouse model of NP-C with an insertion mutation in the NPC1 gene. This model faithfully replicates the human disease in terms of cholesterol and sphingolipid storage, neuropathology, onset of neurological deficits and early death. These mice are hypoandrogenic and bear under-developed reproductive organs suggesting defective biogenesis from cholesterol. Griffin and colleagues proposed that there may also be defective neurosteroidogenesis in the brains of these mice. Neurosteroids act as anxiolytic and anaesthetic agents via ion-gated neurotransmitter channels. The neurosteroid allopregnanolone is thought to play an important role in neuronal growth, differentiation and survival. On this basis, the group postulated that disrupted neurosteroidogenesis, which putatively results from disordered cholesterol trafficking, contributes to the NP-C phenotype. In addition, they proposed that allopregnanolone treatment would alleviate the condition.

Indeed, in this study NP-C mouse brains contained significantly lower levels of neurosteroid as a result of the progressive reduction in expression and activity of neurosteroidogenic enzymes post-natally. Neonatal allopregnanolone treatment slowed the decline of locomotor functions and motor co-ordination, increased Purkinje and granule cell survival, reduced cortical GM2 and GM3 ganglioside accumulation and doubled the life span in NP-C mice. These actions were mediated via the GABAA receptor. Earlier administration of allopregnanolone and continuous treatment regimes proved more effective. The results demonstrate that neurodegeneration in NP-C mice is allopregnanolone dependent. The correlation of improved outcome with earlier administration suggests that allopregnanolone is important in the neurodevelopmental process shortly after birth.

Allopregnanolone represents a promising therapy for the currently

incurable NP-C. It increases the life span of NP-C mice to a similar extent compared to N-butyldeoxynojirimycin, a glucosylceramide synthase inhibitor, currently in clinical trials. However, it has yet to be demonstrated that there is defective adrenal or gonadal steroidogenesis in NP-C children and rodent and human patterns of steroidogenesis are different.

- LMS, SJT

Griffin LD, Gong W, Verot L, Mellon S

Niemann-Pick type C disease involves disrupted neurosteroidogenesis and responds to allopregnanolone.

NATURE MEDICINE

2004 10 (7); 704-711

☆☆☆ RECOMMENDED

AUTISM: an autoimmune disease?

Autism is a complex behavioural syndrome that has fascinated the media and public in recent years. This Portuguese group take on the old story of autoimmunity in autism. They studied the serum from 171 patients with autism compared to 54 controls. Their sera were incubated with SDS-Page blots of protein extracts from a single human brain and antibody binding was visualised with anti-human Ig. There were many varying immunoblot reactivities amongst the samples, requiring complex statistical processing, but overall there were more for autistic children. One reactivity (called "Section 32") most powerfully distinguished autistic children from controls. This antibody identifies a protein of around 20kDa. The investigators speculated that this might be one of the MBP isoforms; however all attempts to demonstrate that failed.

So children with autism produce more antibodies against brain components than controls, and against one unidentified protein in particular. Fascinating stuff, but what does it mean? Are these antibodies pathogenic? Or responses to neuronal damage? Or even neuro-protective? Only interventional and animal studies can answer these questions. The use of IVIG to treat autism in the late 1990s was deemed largely ineffective, but perhaps we should revisit that. And, I am sure, Susana Silva and colleagues are squirting Section 32 into rodents right now and waiting for the first signs....



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The Epilepsy Research
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What the anti-MMR lobby will make of it all, I dread to think. - *AJC Silva SC, Correia C, Fesel C, Barreto M, Coutinho AM, Marques C, Miguel TS, Ataide A, Bento C, Borges L, Oliveira G, Vicente AM. Autoantibody repertoires to brain tissue in autism nuclear families. JOURNAL OF NEUROIMMUNOLOGY 2004;152(1-2):176-82*

COGNITION: Medial frontal lobe damage and 'Theory of Mind'

This rigorous neuropsychological case-study examines the neural basis of 'theory of mind', a cognitive function currently of great interest. The paper reaches specific conclusions on 'theory of mind' and also provides a useful reminder that, in the localisation of cerebral function, findings from functional imaging and lesion studies must be considered in parallel.

When we explain or predict the behaviour of others by ascribing to them certain beliefs, desires or fears we seem to construct a framework of mental states, i.e. a 'theory of mind' (ToM). The concept of ToM has proven useful in interpreting social difficulties experienced in autism. More recently, tests that tap into ToM function have been found to be informative in cases of frontal lobe damage, particularly frontal-type dementia.

Bird and colleagues describe a case of bilateral anterior cerebral territory infarction, where the damaged anterior parasagittal region bilaterally corresponds to the key region implicated in functional imaging studies of ToM. The surprising finding is that the subject performed within the normal range on four out of five administered ToM tests. The single exception was in a task requiring a judgement on violations of social norms; she judged fewer of the violations to have been embarrassing than did controls. The findings are particularly valuable as the lesion here is well circumscribed. This contrasts with previous cases studied where neuro-axonal injury, seizure-related damage or neurodegeneration are likely to have occurred even in areas where scan appearances were normal. The main limitation is that inferences are being drawn from a single case. For instance, although evidence is offered that the subject's premorbid function was essentially normal, one could argue that her occupation as a teacher would have allowed her to develop superior ToM abilities. The authors do not dwell on the additional complication that ToM, though beguiling as a concept, may well not represent a unitary function.

It is concluded that the antero-medial frontal region, damaged in this case, is not necessary for ToM, although activation of the region in functional studies suggests that it may be sufficient. - *RD*

Bird CM, Castelli F, Malik O, Frith U, and Husain M.

The impact of extensive medial frontal lobe damage on 'Theory of Mind' and cognition.

BRAIN

2004; 127: 914-928

EPILEPSY: Vacuum cleaner reveals a role for circadian genes in epilepsy

The study of a family of transcription factors has inadvertently revealed a link between circadian genes and epilepsy, with the help of a vacuum cleaner.

The PARbZIP protein family consists of three transcription factors DBP, HLF, TEF, the levels of which oscillate according to circadian rhythm. They accumulate at high concentrations in tissues with high amplitude clock gene expression, including the liver and the suprachiasmatic nucleus (SCN; the major mammalian circadian pacemaker). In the brain, the clock gene expression cycles at low amplitude, so that the level of these transcription factors does not fluctuate significantly. Schibler and colleagues were interested in identifying the physiological role of these PARbZIP transcription factors, which have been well conserved throughout mammalian evolution.

Single, double and triple knock-out mice of the three PARbZIP transcription factors were generated and were all anatomically normal and fertile. However, the triple mutant mice died prematurely. The reason for such a dramatic reduction in life span was a mystery until it was noted that the mice died predominantly on Mondays and Thursdays when the animal facility was cleaned. It became clear that the noisy vacuum cleaner was inducing lethal audiogenic seizures in these mice. EEG recordings confirmed this abnormal brain activity and also revealed the susceptibility of the triple mutants to spontaneous generalised tonic-clonic seizures.

The pyridoxal kinase (Pdxk) enzyme is proposed to explain the link between PARbZIP transcription factors and epilepsy. Pdxk was identified by transcriptome profiling as a target gene for the PARbZIP family. It is involved in the conversion of vitamin B6 derivatives to pyridoxal phosphate, a coenzyme important in neurotransmitter homeostasis. Consistent with this finding, Schibler demonstrated down-regulation of Pdxk expression and subsequent reduction in serotonin and dopamine concentrations in the brains of triple knock-out mice. It is widely accepted that such an imbalance in neuro-

transmitter levels results in epileptic seizures and thus represents a plausible explanation for PARbZIP deficiency in causing epilepsy. This study demonstrates the crucial role the PARbZIP transcription factors play in keeping Pdxk levels within narrow limits in the brain and preventing life-threatening seizures.

This study of triple PARbZIP knock-out mice is clearly of relevance to epilepsy in humans: first, because vitamin B6 deficiency is a known cause of epilepsy. Second, the recessive disease, Unverricht-Lundborg disease (ULD) is caused by mutations in the cystatin B gene, which lies adjacent to Pdxk. The most common mutation causing ULD is a dodecamer expansion in the promoter region. It is therefore conceivable that this mutation also alters Pdxk expression. This mouse is a good model of human disease and may be useful to study pathogenesis and therapeutics - *LMS, SJT*

Gachon F, Fonjallaz P, Damiola F, Gos P, Kodama T, Zakany J, Duboule D, Petit B, Tafti M, Schibler U.

The loss of circadian PARbZIP transcription factors results in epilepsy.

GENES AND DEVELOPMENT

2004 18; 1397- 1412

PAIN: A "hot" neuropathic pain model for fMRI?

People living with nerve damage (neuropathy) can experience painful sensations during transient brushing of the skin e.g. from bed sheets at night or from clothes during movement.

One model of neuropathic pain combines two methods, physical stimulation (heat), and chemical stimulation (topical capsaicin, the active ingredient of chilli pepper) to elicit measurable and reliable areas of "allodynia" - pain induced by an innocuous stimulus. Using this combined model allodynia can be studied for longer than when either method is applied alone. As it is feasible to rekindle allodynia on demand by reapplying heat, it is timely to investigate the model using neuroimaging.

Eleven healthy subjects participated, all right handed. Their left forearm skin was pre-exposed to measured applications of heat and chemical sensitisation. During the functional magnetic resonance imaging (fMRI) experiment, a hand-held brush mechanically stimulated allodynia on the left, and following scanning, sensory testing was used to confirm the allodynia to touch in given areas. The right, untreated, forearm (control site) was compared within the same fMRI brushing paradigm.

Brushing led to different brain activations depending upon whether skin was allodynic or not. Brushing not associated with pain resulted in contralateral S1, PA and insula activation and bilateral S2 activation. Allodynia evoked by brushing resulted in partially overlapping activations, though activation was found in the contralateral inferior frontal cortex (IFC) and was ipsilateral in the insula. "Direct comparison between nonpainful brushing and brush-evoked allodynia revealed significant increases in blood oxygenation level dependent (BOLD) signals in contralateral S1, PA, IFC and bilateral S2/insula during allodynia".

How well does this experimental model simulate neuropathic pain? We do not know. We will learn more by refining the repeatability of such paradigms and examining the effects of existing pharmacological treatments on them.

-*LAJ*

Maihöfner C, Schmelz M, Forster C, Neundörfer B, and Handwerker H.

Neural activation during experimental allodynia: a functional magnetic resonance imaging study.

EUROPEAN JOURNAL OF NEUROSCIENCE

2004; 19: 3211-3218, 2004

NEUROIMMUNOLOGY: Lupus in the midbrain

Cerebral lupus is a curious disease. It is not easy to understand the pathogenesis of the common symptoms of cognitive impairment, low mood and poor attention in the face of normal imaging. This study from Canada helps just a little. It focuses on the MRL-lpr animal model of lupus, which has a lpr mutation on chromosome 19 and a defective Fas receptor, leading to failure of deletion of autoreactive T cells. These animals develop florid lupus by three months and are dead three months later. The authors showed that apomorphine injections induce rotational behaviour in these animals, suggesting nigrostriatal damage. Pathologically, there was a loss of TH-positive cells and reduced neuronal survival (demonstrated by increased FJB staining) in the substantia nigra pars compacta. There were no accompanying inflammatory cells, suggesting the mechanism of death was degenerative (and CSF from diseased animals did kill neural progenitor cells in vitro). But immunosuppression of the animals with cyclophosphamide did prevent these changes.

Interesting maybe, but Parkinsonism is an incredibly uncommon feature of lupus (except perhaps in children). However, this animal work begins to resonate when the investigators move on to behavioural tests of their mice. Compared to control animals the MRL-lpr mice showed anhedonia (losing interest for sucrose drinks), reduced motor activity over 30 minutes and

increased "behavioural despair" (spending greater time floating in a no-escape swimming task). Now, that is more like what our patients are telling us. Very unfortunately, the investigators did not examine the effects of immunosuppression on these behaviours, but the implication from the pathology studies would be that they would improve.

So, contrary to prevailing opinion, the cognitive complaints of people with lupus may be due to focal midbrain degeneration and may respond to immunosuppression. All well and good but –if so- why don't we see more Parkinsonism in lupus? Cerebral lupus is a curious disease. -*AJC Ballok DA, Earls AM, Krasnik C, Hoffman SA, Sakic B. Autoimmune-induced damage of the midbrain dopaminergic system in lupus-prone mice. JOURNAL OF NEUROIMMUNOLOGY 2004;152(1-2):83-97.*

EPILEPSY: Marijuana use..... well would you?

Animal studies have shown a mild antiepileptic effect of cannabinoids although a single trial in humans has been inconclusive. The authors sought to establish the extent of cannabis use in 241 patients in an outpatient database. Only 160 could be contacted and of these 136 had ever used marijuana. Eighteen (13%) were frequent users (48 days in the last year) and 11 (8.1%) were heavy users (more than 182 days in the last year). Four met the DSM-IV criteria for marijuana dependence.

In contrast to use in the general population, the likelihood of using marijuana was not affected by gender or unemployment. It was increased if epilepsy duration was longer and if seizures were frequent. The only statistically significant association was with use of other illicit drugs in the previous year. There was no association with alcohol. 24% of patients believed marijuana benefited their epilepsy.

A question with this kind of study is do patients tell the truth when asked about illegal activities – well would you? Taken at face value a pragmatic line is that use of marijuana in epilepsy probably has little effect either way on epilepsy severity. The most important points here then are the increased use of neurotoxic drugs of abuse in patients who admit to marijuana use and the belief of some patients in the therapeutic benefits of marijuana. - *MRAM Gross DW, Hamm J, Ashworth NL, Quigley D. Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy centre.*

NEUROLOGY
2004;62:2095-2097.

☆☆☆ RECOMMENDED

PARKINSON'S DISEASE: How on earth does dopamine therapy help?

The management of Parkinson's disease (PD) is complex but most people would agree that dopaminergic therapies are helpful because they stimulate the striatal output neurons through either D1 or D2 receptors. However a recent series of papers suggest that this may only be part of the story.

In the first article from the group of Calabresi, the actions of L-dopa were investigated in the unilateral 6-OHDA rat model of PD. This group, using detailed neurophysiological recordings, found that the actions of L-dopa may be mediated by modification of the glutaminergic corticostriatal projection. In particular they report that the relative glutaminergic hyperactivity that occurs with dopaminergic denervation can be reversed by L-dopa through a presynaptic D2 receptor on the corticostriatal terminals. This study follows up on an earlier report from this group (reported last year – see ACNR 3.3) on the basis of drug induced dyskinesias in PD, and highlights the complex actions of L-dopa therapy in this condition. Indeed this study (as previous) has shown curiously that using an identical lesion and L-dopa dosing regime produces two distinct responses in rats – one group of rats show a therapeutic response, whilst the other show no such benefit owing to the development of dyskinesias. Why such genetically homogenous animals develop such varied responses is unknown, but it may be telling us something about the heterogeneity of treatment response in patients with this condition.

In the other two papers the emphasis shifts to the effects of dopamine therapies on the endogenous neural precursor cell (NPC) found in the subventricular zone (SVZ) of the adult brain. We hypothesised 3 years ago in the *Lancet* that abnormalities in the endogenous NPC may contribute to the genesis and evolution of neurodegenerative disorders, and these papers go some way to supporting this. In the first of these papers Baker *et al* show that 6-OHDA lesion of the nigrostriatal pathway in adult mice reduces the number of proliferating NPCs in the subventricular zone of the lateral ventricle in the striatum. This observation compliments the data presented in the much more extensive study of Höglinger *et al*. This latter study shows that

the midbrain dopaminergic projection includes an innervation to the SVZ, and that manipulation of this innervation alters the kinetics of NPC proliferation. This action is mediated through a D2 receptor, and is such that the loss of dopamine in PD results in reduced SVZ NPC proliferation – the consequences of which are unknown but may contribute to olfactory deficits seen in this condition (albeit given the recent doubts about the existence of the rostral migratory stream in adult humans – see ACNR 4.2).

These articles are therefore thought provoking and raise all sorts of questions about the best management of this common neurological condition, not only about L-dopa but also whether we should be using growth factors and cell replacement strategies. - *RAB Picconi B, Centonze D, Rossi S, Bernardi G, Calabresi P. Therapeutic doses of L-dopa reverse hypersensitivity of corticostriatal D2-dopamine receptors and glutamatergic overactivity in experimental parkinsonism. BRAIN 2004;127: 1661-1669*

Baker SA, Baker KA, Hagg T.
Dopaminergic nigrostriatal projections regulate neural precursor proliferation in the adult mouse subventricular zone.
EUROPEAN JOURNAL OF NEUROSCIENCE
2004;20:575-579.

Höglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, Hirsch EC.
Dopamine depletion impairs precursor cell proliferation in Parkinson's disease.
NATURE NEUROSCIENCE.
2004. Epub advanced on line publication.

☆☆☆ RECOMMENDED

REHABILITATION: Cortical reorganisation starts straight away after cerebral ischaemia

One issue for rehabilitation of patients with cerebral infarcts is timing. When is the best time to start rehabilitation? It is not clear whether the potential for beneficial cortical plasticity is greater early after injury or whether there are dangers in starting training early after stroke. Certainly increased excitability of the cortical area surrounding the infarct has been observed in animal models in the early days after a stroke. This has been seen as a sign that there is greater potential for cortical plasticity as a response to brain damage immediately after stroke. However there is also a cautionary school of thought that links the raised excitability to dangerous excitotoxic effects of glutamate released in the ischemic cascade. Now a group in Tokyo have been the first to find rapid plastic changes along with increased excitability in the peri-infarct cortex occurring during the first few hours after lesioning.

Using rats with photochemically induced ischemia in the somatosensory cortex, Fujioka *et al* recorded cortical evoked potentials to single and paired electrical stimuli of the ulnar nerve before and after 1,2,4 and 6 hours following infarction. In addition they mapped the receptive fields in the cortex that corresponded to touch on the forepaw skin using a von Frey hair type probe. The amplitude of evoked potentials demonstrated increased excitability of the peri-infarct area as early as one hour after injury and increased over the observations collected up to six hours. The size of receptive fields in the forepaw also began increasing within one hour of the infarct and kept increasing in correspondence with excitability changes over the subsequent hours.

We are a little way off determining the best biological time for rehabilitation as yet. Certainly many patients are too ill for very active rehabilitation in the early days, let alone hours, after stroke and some are not psychologically ready. But in future maybe this early plasticity could be used to improve outcome for some patients with stroke. - *AJT Fujioka H, Kaneko H, Suzuki SS, Mabuchi K. Hyperexcitability-Associated Rapid Plasticity After a Focal Cerebral Ischemia. STROKE 2004: 35: e346-e348*

EPILEPSY: Propofol treatment of status epilepticus

Status epilepticus needing anaesthesia is common enough to be a major medical emergency, which all neurologists and many other physicians encounter, but not common enough for there to be decent comparative studies of the treatments available. Consequently we rely on retrospective reviews of practice, such as this one, which nevertheless, provide useful information. Eighteen episodes of refractory convulsive status epilepticus affected 15 patients. Fourteen of these occurred in 11 patients with a previous history of epilepsy. Triggers were identified in 9; non-compliance in 4, electrolyte imbalance in 3, and alcohol intoxication and cerebral hypoperfusion in 1 each. In all, 22 of 31 episodes were in patients with previous epilepsy. Focal convulsive status, whether focal motor status or non-convulsive status, was nearly always due to an obvious lesion such as a glioma or an acute neurological insult such as viral encephalitis.

Acute treatment in this unit was usually with clonazepam and phenytoin. All patients had failed this treatment in order to enter the study and were treated with propofol to achieve burst suppression. Median duration of treatment was 3 days and length of stay in ITU was 7 days. Hypotension requiring treatment affected half of patients. Five patients experienced at least two recurrences of status on attempts to wean off medication and one developed hyperlipidaemia, necessitating change of treatment. These patients were switched to thiopental. Seven patients died, one from GI haemorrhage after leaving ITU and 6 on the ITU. Three of the patients who died had required thiopental as well as propofol. Two fatalities were in convulsive status patients (11%) and five in the focal cases (38%), probably reflecting the higher incidence of acute pathology. Of the 21 patients who survived 24 episodes, 16 had no sequelae and mild anterograde memory impairment affected 5. Critical care neuropathy affected two patients and one had a severe post-anoxic encephalopathy. Transient tremor affect 10 patients on weaning from propofol and one had a focal upper limb dystonia.

This study supports previous studies in demonstrating that aetiology is the main determinant of death in aggressively treated status epilepticus. Focal presentations reflected acute aetiologies and had a poorer prognosis. Propofol seemed to be effective in the majority of cases, and may have helped to keep ITU admission short and caused few drug-related problems. It seems a reasonable first line drug but this area is calling out for a properly designed comparative study of barbiturates and propofol. -MRAM

Rosetti A, Reichard MD, Schaller M-D, Despland P-A, Bogousslavsky J.

Propofol treatment of refractory status epilepticus: a study of 31 episodes.

EPILEPSIA

2004;45:757-763

EPILEPSY: epilepsy, pseudoseizures & personality

Many studies have looked at whether personality traits can be used to predict whether a patient has epilepsy or psychogenic non-epileptic seizures. The current study used a basic questionnaire (DAPP-BQ) which assesses 18 traits and four higher order dimensions of personality pathology. Apparently human personality can be described in combinations of 5 basic traits even across different cultures. The big 5 are: neuroticism; extraversion; agreeableness; conscientiousness and openness to experience. The authors compared traits in patient with PNES, epilepsy and normal controls. Only 60% (n=85) of PNES patients and 54% (n=64) of epilepsy patients responded. PNES patients had higher scores than epilepsy patients on emotional dysregulation scales. These include measures of anxiety, identity problems, social avoidance, affective lability, submissiveness, etc. They had higher scores than controls on measures of dissociative behaviour eg. stimulus seeking, rule breaking, rejection of others and callousness and also higher scores on inhibitedness and compulsivity. On all these measures they did not differ significantly from epilepsy patients.

The authors then performed cluster analysis of the scores in PNES patients and found two large clusters, a small cluster of four patients and a single outlier not conforming to any of these groups. Cluster 1 had high scores across the board, something also seen in patients with personality disorder. Cluster 2 had increased compulsivity scores but normal scores in the other areas, as seen in compulsive disorders. Cluster 3 had high scores in emotional dysregulation, inhibitedness and compulsivity but not dissociative behaviour scores, which resembles avoidant personality disorder. Remission of PNES in cluster 1 was 14% and 40% in cluster 2 at follow-up.

So can personality traits be used in the diagnosis of PNES versus epilepsy? The purist would say no and that the seizure must be diagnosed in its own right but how often is the electrographic diagnosis merely the confirmation of a very strong clinical suspicion and what gives that clinical suspicion? I maintain there are certain seizure-related features but also the manner in which how the history is delivered, and the impression that one is dealing with a disturbed patient rather than an anxious or depressed patient, that also helps to give the diagnosis. I don't know how you put that in a scale. What this study does is to start to address the subdivisions of PNES in terms of psychological profile which may have implications in tailoring treatment and also seems to have prognostic value. -MRAM

Reuber M, Pukrop R, Derfuss R, Elger CE.

Multi-dimensional assessment of personality in patients with psychogenic non-epileptic seizures.

JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY

2004;75:743-8

SPASTICITY: Muscle overactivity in the upper motor neuron syndrome

This article is actually more interesting than the title suggests as the authors frequently illustrate the clinical relevance of basic physiology and the role of oral anti-spasticity agents in the upper motor neurone (UMN) syndrome. It is one of a series of five review articles on spasticity in this issue, covering new European Consensus Guidelines on treatment, focal treatments, intrathecal baclofen and physical/surgical options.

The article opens with what clinicians mean and understand by the term "spasticity". The persistent ambiguity of terminology is reflected in 43 studies that they examined in which they found 229 outcome measures in a variety of nine clinical and physiological categories. The authors (both Americans despite the journal title) cover a wide range of positive phenomena of the UMN syndrome: stretch reflexes, clonus, flexor and extensor spasms, co-contraction, spastic dystonia and associated reactions. They also provide a useful discussion on the importance of muscle rheology (soft tissue changes) and the difficulty in distinguishing it from spasticity clinically.

I found it really annoying that the numerous figures were invariably on preceding pages so one had to constantly flick pages back and forth whilst reading (clearly they don't have the standard of editorialship of ACNR!). And despite frequent references to his own work by one of the authors this is a useful brush-up of the pathophysiology of the UMN syndrome and mechanisms of action of oral agents. -JMCF
NH Mayer, RM Herman.

Phenomenology of muscle overactivity in the upper motor neuron syndrome.

EUROPA MEDICOPHYSICA

2004;40:85-110

Computer Technology to Support the Treatment of Aphasia

A recent edition of the international interdisciplinary journal, *Aphasiology* concentrated on the role of computers in the treatment and lives of people with aphasia. The issue was edited by Brian Petheram¹, a systems analyst from the University of the West of England, who has had a long standing interest in the role of computers to treat and manage those with aphasia.

Aphasia is usually an acquired language and communication disorder associated with stroke or head injury but also seen in some neurodegenerative conditions. Persons with aphasia (term is used interchangeably with dysphasia) have difficulty with understanding and expressing in both verbal and written forms.

In the 1970s and '80s there was increasing evidence that generalised speech and language therapy, whilst benefitting some patients, did not offer an advantage compared to that achieved by untrained people providing stimulation and conversation to the patient. Later investigations of more specific speech therapy demonstrated that targeted intensive therapy could have an impact in regaining and using language. Unfortunately there are few services that can provide the form of intervention that is suggested to be the most effective. Thus many researchers have turned to how such specific treatment can be provided when resources are limited. In the editorial Brian Petheram¹ charts the development of the use of computers with aphasic patients. He draws attention to the fact that at first, in the 1980's, most of the software was somewhat rigid and generalised so that whilst one could provide more treatment to aphasic patients it was difficult to target the particular deficit of a patient. More recently, and within this special issue, studies have involved development and evaluation of software which can support individualised treatment. Interestingly one of the papers (Doesborgh et al)² describes an approach which allows patients to explore different strategies that suit them and their aphasia. The computer programme (Multicue) offers a variety of cues for improving word finding and stimulates the user's independence by encouraging them to discover for themselves which cueing strategies are most useful. This paper describes a total of eighteen individuals with aphasia who were randomised to receiving either treatment (n=8) or not (n=10). The treated group (using Multicue) had improved word finding as identified on the Boston Naming Test. However, this positive finding was not reflected in tests of functional communication gain. In the same issue, Mortley et al³ provided speech and language therapy to seven participants who were all at least two years post stroke and received their intervention entirely at home on computer via the Internet. This study, which took a single case design, indicated that the mode of therapy was efficacious (i.e. there was a measurable improvement in word retrieval skills) and acceptable with patients in interview, being both positive about the approach and adopting its use intensively. However, information on generalisation was limited. Wertz and Katz⁴ review a number of different small computer based aphasia therapy studies using the Level of Evidence Scale developed by the American Academy of Neurology (1994) with the majority being Phase One studies (8 detailed in this paper) compared to three Phase Two and one Phase Three study. These

authors conclude that while several Phase One and Phase Two studies imply that computer provided treatment is active in the treatment of people with aphasia, evidence to support the efficacy of computerised treatment for adults is at present based on one single Phase Three study. The authors call for more Phase Three studies and also underline the importance of developing further research which will demonstrate the effectiveness and efficiency of computerised treatments.

Other papers within this edition do not necessarily explore the use of computers in providing treatment for aphasia but describe methods by which computers can support an aphasic person in their communication. However, Mieke van de Sandt⁵ highlights that most assistive technology has been developed for the use of persons with dysarthria, whilst those with aphasia who are trained to use augmentative strategies usually are introduced to non-computerised approaches. However, she argues that the factors influencing success and failure of low tech augmentative communication are relevant to the development of high tech communication aids. Now that computers can be tailored for more flexible use and approaches to prediction have developed, there will be more opportunities for allowing people with a range of cognitive and language problems to communicate more effectively. Needless to say, more detailed information regarding the retained skills of aphasic patients and their needs will assist the development of appropriate hardware, software and training programmes.

Finally the editor concludes that a lot of the foundation work to this area has been completed over the last decade. In particular the nature of aphasia and content of therapy, along with patient and carer views, has become better understood and so it is likely that over the next decade we will see real advances in the area of computer supported therapy and management for aphasic patients.- Prof. Pam Enderby

APHASIOLOGY
2004: 18 : 3

Additional References

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